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Acute Febrile Encephalopathy in Children: Etiology, Clinical Presentation and Outcome

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ABSTRACT

Background: Fever and altered sensorium constitute a medical emergency in children. Early recognition, accurate diagnosis and timely management may help in reducing the morbidity and mortality in acute febrile encephalopathy (AFE).

Aim: To study etiology, clinical presentation and outcome in children presenting with acute febrile encephalopathy.

Methods: This prospective observational cohort study was conducted in a tertiary care centre over the duration of one year (2016 to 2017). Consecutive patients (age group of one month to 12 years) presenting with fever of ≤ 2 weeks duration and altered mental status were enrolled. The clinical features were noted and patients were followed up through the duration of hospital stay (wards & intensive care unit). Etiology and clinical features were listed as percentage of total cases. Risk factors for mortality were determined using chi-square test.

Results: 120 children were enrolled. Besides fever and altered sensorium, convulsions (70%) and meningeal signs (38.3%) were common clinical features. Tubercular meningitis (33.3%) was the most common cause followed by viral encephalitis (24.2%), bacterial meningitis (9.2%) and cerebral malaria (5.8%). Mortality was 16.7% with neuro-morbidity seen in 45% of the cases. Longer duration of hospital stay (≥ 28 days), longer duration of PICU stay (> 14 days), longer duration of mechanical ventilation (≥ 7 days) and low Glasgow coma score (GCS< 8) were risk factors associated with higher mortality.

Conclusions: Infectious causes were the commonest cause of AFE. AFE has a high rate of neuro-morbidity. Early identification of high risk factors may help to reduce the mortality.

Keywords: Altered sensorium, Child, Encephalitis, Meningitis, Neuromorbidity, Tubercular.

Key Message: Most common etiology for children presenting with acute febrile encephalopathy (to our institute) was tubercular meningitis (TBM) followed by viral encephalitis, bacterial meningitis and cerebral malaria. The mortality was 16.7% with 45% neuromorbidity.

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INTRODUCTION

Acute febrile encephalopathy (AFE) is a term used for children presenting with altered sensorium either accompanying (or following) a short febrile illness.[1] Despite a lot of epidemiological investigations, the presentation of AFE has often remained a mystery and very few Indian studies exist on this topic.[2] The changing clinical presentations have also posed a challenge in the optimal management of patients with AFE. Recognizing early signs of encephalopathy is

important as these patients put heavy demands on Pediatric intensive care units (PICUs) and rehabilitation resources.[3] The etiology of AFE also differ according to geographical regions; hence appropriate and efficient protocols (for investigations and management) require proper understanding of the various potential etiologies.[4] There has been a paucity of Indian studies describing the etiology of AFE as well.[3] Early recognition, efficient decision making and rapid institution of therapy can be life-saving and can also help the physician to nurture these children in a better way.[1] We aimed to study the causes, clinical presentation and outcome of children presenting with acute febrile encephalopathy (AFE) in a metropolitan city of Western part of India.

MATERIALS & METHODS

Ours was a prospective, observational cohort study in patients admitted to the Pediatric intensive care unit (PICU) and Pediatric inpatient wards of tertiary care hospital affiliated to a premier medical college from a metropolitan city of Western part of India. The study was initiated after permission from the Institutional Ethics Committee (IEC) and case enrolment was done after a written informed consent from the parent/guardian. Since the patients with encephalopathy were in altered sensorium, waiver of assent was taken from the institutional ethics committee.

We included all children presenting with acute febrile encephalopathy (AFE) aged one month to 12 years with (i) Duration of illness of < 2 weeks (acute), (ii) Fever/ history of fever at onset of the illness, and (iii) altered mental state (Glasgow Coma Score- GCS< 15). We excluded patients with febrile convulsions, hypoxic ischemic encephalopathy, cerebral palsy, inborn errors of metabolism, neuro-regression and mental retardation. The sample size was calculated as per the average annual admissions of cases of AFE in our hospital (convenience sampling). All consecutive patients fulfilling the inclusion criteria were enrolled with each patient being in the study for their complete duration of stay in the Pediatric wards and / or Pediatric intensive care unit - PICU (until discharge or death). Detailed medical history, clinical examination findings and investigations were recorded in a pre-designed case record form. The etiology was based upon the clinical features, the investigations and the final diagnosis made by the treating physician. The final outcome was recorded in terms of neuro-morbidity (defined as presence of abnormal neurological findings like tone / power disturbances and/ or altered sensorium) and mortality.

Statistical methods

The etiologies, clinical features and outcome were enlisted as percentage of the total cases. The risk factors for mortality were determined using chi-square test. Qualitative data was represented in form of frequency and percentage. Association between qualitative variables for nominal data like sex, history of convulsion, types of convulsions, clinical signs, computed tomography (CT), magnetic resonance imaging (MRI) and cerebrospinal fluid examination (CSF) findings, final diagnosis, outcome (survival/death) and recovery status (if survival; in terms of complete or incomplete or no recovery), was assessed by Chi-Square test, with continuity correction for all 2 X 2 tables and by Fisher's Exact test for all 2 X 2 tables where Chi-Square test was not valid due to small counts. Ordinal data [Glasgow coma score (GCS)] and quantitative data (age, duration of fever, duration of hospital stay, duration of PICU stay and duration of mechanical ventilation) were represented using mean ± SD and median and interquartile range. Appropriate statistical software/s (MS Excel, PSPP version 1.0.1) were used for statistical analysis.

RESULTS

A total of 120 patients were enrolled consecutively over a period of 12 months (October 2016 to September 2017). Most patients were from age group of less than 2 years - 33 out of 120 (27.5%), followed by 4 to 6 years - 27 patients (22.5%). The mean age was 4.8 years with median of 5 years. There was male preponderance (males: females = 60: 40). Most patients had a hospital stay of < 14 days (68/120 cases, i.e. 56.7%). Mean duration of hospital stay was 15.02 days with median of 12 days. 44 (36.7%) patients required intensive care in Pediatric intensive care unit (PICU). Mean duration of PICU stay was 12.68 days (median 5 days). Out of the 44 cases admitted to PICU, 37 patients required mechanical ventilation for a mean duration of 13.54 days.

Table I describes the study population in details while Table II gives the etiological distribution of the cases of AFE. We had 40 cases (33%) of tubercular meningitis (TBM), followed by viral encephalitis (24.2%; 29 cases), bacterial meningitis (9.2%; 11 cases) and cerebral malaria (5.8%; 7 patients) as the commonest diagnosis. In terms of clinical presentation (Table III) the mean duration of fever

was 7.75 days and 33 (27.5%) cases had GCS of less than 8 (mean GCS 9.02 ± 2.71). 84 (70%) patients had convulsions at presentation (most common being generalized tonic-clonic convulsions in 62 cases) while 14 patients presented with status epilepticus. Other less common signs like meningeal signs, neurological deficits and abnormal movements were seen in 38.3% (46 cases), 19.2% (23 cases) and 11.7% (14 cases) respectively.

20 patients died (mortality 16.7%) in this study. The number of deaths as per etiology were: tubercular meningitis - 8, viral encephalitis - 5, bacterial meningitis - 1, cerebral malaria - 0, hepatic encephalopathy- 3, intracranial bleed - 0 and others - 3 cases. Of the 100 patients who survived, 54 patients had neuro-morbidity while 46 recovered completely. Among the 54 neuromorbid patients, 40 children had incomplete recovery, while 14 patients had no recovery at all. Incomplete recovery was seen mostly in cases of intracranial bleed and

Table I: Details of study population.

Variable	Maximum and Minimum	Mean with SD and Median
Age	0.1 – 12 years	Mean: 4.8; SD- 3.46 years; Median: 5 years
Duration of hospital stay	1-75 days	Mean: 15.02; SD-11.99 days; Median: 12 days
Duration of PICU stay	1-60 days	Mean: 12.68;SD-14.81days; Median: 5 days
Duration of mechanical ventilation	1-53 days	Mean:13.54; SD-16.02 days; Median: 5 days

Note: SD = Standard deviation

Table II: Etiological distribution of cases of acute febrile encephalopathy (AFE).

Final diagnosis	Number	Percentage
Tubercular (TB) meningitis	40	33.3%
Viral encephalitis	29	24.2%
Bacterial meningitis	11	9.2%
Cerebral malaria	7	5.8%
Hepatic encephalopathy	4	3.3%
Intracranial bleed	4	3.3%
Rabies encephalitis	2	1.7%
Epileptic encephalopathy	2	1.7%
Acute necrotising encephalopathy	1	0.8%
Acute demyelinating encephalo-myelitis (ADEM)	2	1.7%
Autoimmune encephalitis	1	0.8%
Brain abscess	1	0.8%
Dengue encephalopathy	3	2.5%
Diabetic ketoacidosis	1	0.8%
FIRES (Fever induced refractory epilepsy syndrome)	1	0.8%
Haemorrhagic encephalopathy	1	0.8%
HIV encephalopathy	1	0.8%
Hypernatremic dehydration	1	0.8%
Hypertensive encephalopathy	1	0.8%
Hyponatremia	1	0.8%
Infected dermoid cyst	1	0.8%
Moya Moya disease	1	0.8%
Pilocytic astrocytoma with meningitis	1	0.8%
Rassmussen encephalopathy	1	0.8%
Subacute sclerosing panencephalitis (SSPE)	1	0.8%
Uremic encephalopathy	1	0.8%
Total	120	100.0%

Table III: Details of clinical presentation.

Symptom/ Sign	Number (total 120)	Percentage
Fever	120	100%
Altered sensorium	120	100%
GCS < 8	33	27.5%
GCS ≥ 8	87	72.5%
Convulsions	84	70%
Meningeal signs	46	38.3%
Neurological deficits	23	19.2%
Abnormal movements	14	11.7%

Note: GCS = Glasgow coma score.

viral encephalitis. All the cases of cerebral malaria showed complete recovery.

The risk factors affecting mortality in AFE are presented in Table IV. Longer duration of hospital stay (≥ 28 days), longer duration of PICU stay (> 14 days), longer duration of mechanical ventilation (≥ 7 days) and lower GCS (< 8) increased mortality on univariate analysis. Days of hospital stay and duration of PICU stay were found to be significantly associated with higher mortality on binary logistic regression analysis. Etiological diagnosis and clinical presentation did not affect the clinical outcome. However, convulsions were significantly associated with presence of neuro-morbidity.

Table IV: Risk factors for mortality in AFE.

Risk factor	Survived	Died	P value
Age			
<6 years	63	12	0.8 (NS)
≥ 6 years	37	8	
Sex			
Males	14	58	0.453 (NS)
Females	6	42	
Duration of hospital stay ≥ 28 days	7	7	0.0017 (S)
Duration of hospital stay < 28 days	93	13	
Duration of PICU stay > 14 days	4	9	0.013 (S)
Duration of PICU stay ≤ 14 days	22	9	
Days of mechanical ventilation ≥ 7 days	3	12	0.023 (S)
Days of mechanical ventilation<7 days	14	8	
GCS < 8	20	13	0.00012 (S)
GCS ≥ 8	80	7	
Convulsions	70	14	1.000 (NS)

Note: NS = Statistically not significant; S = Statistically significant ($p < 0.05$).

Table V: Etiology, mortality and risk factors affecting mortality across various studies.

Author (year of publication)	Type of population & Number(N*)	Common etiologies (%)	Mortality	Risk factors increasing mortality
Our study	AFE (N=120)	Tuberculous meningitis (33.3%), viral encephalitis (24.2%), bacterial meningitis (9.2%) & cerebral malaria (5.8%).	16.7%	Longer duration of hospital stay (≥ 28 days), longer duration of PICU stay (> 14 days), longer duration of mechanical ventilation (≥ 7 days) & lower GCS (< 8).
Ahmad et al. (2017)[9]	Non traumatic coma (N=61)	Infectious causes (41%), toxic-metabolic causes (26.2%), status-epilepticus 16.4% & structural CNS lesions in 8.2%.	33.9%	Age ≤ 3 years, poor pulse volume, hypotension, abnormal respiratory pattern, abnormal pupils, absent corneal reflex, abnormal extra-ocular movements, lower modified GCS & papilledema.
Kumar et al. (2017)[6]	AFE (N=234)	Viral encephalitis (45.8%), pyogenic meningitis (42%), cerebral malaria (7.5%) & tubercular meningitis (3.7%).	Not studied	Not studied.
Bokade et al. (2014)[2]	AFE (N=176)	Viral encephalitis (46.59%), bacterial meningitis (22.16%), cerebral malaria (15.9%) & tubercular meningitis (15.35%).	19.31%	Shock, severe anemia, bradycardia, Glasgow coma score (< 8) & refractory seizures.
Ahmed et al. (2011)[10]	Non-traumatic coma (N=100)	Acute bacterial meningitis (31%), cerebral malaria (29%), viral encephalitis (18%) & tubercular meningitis (12%).	29%	Hypothermia, hypotension, altered breathing pattern, non- reactive pupils, low GCS, hypotonia, hyporeflexia & muscle power score of two.
Anga et al. (2010)[7]	AFE (N=149)	Bacterial meningitis (22.1%), tubercular meningitis (15.4%)& cerebral malaria (2%).	8.93%	GCS, Traumatic Brain Score & multiple convulsions.

Note: N = Total number of cases/ population; GCS = Glasgow coma score.

DISCUSSION

The etiology of AFE is varied. In our study, tuberculous meningitis (33.3%) was found to be the most common etiology of AFE followed by viral encephalitis (24.2%), bacterial meningitis (9.2%) and cerebral malaria (5.8%). This was in contrast to other studies where viral encephalitis was the most common cause of AFE. Modi *et al.* (2015), reported viral encephalitis (40%) to be the commonest cause of AFE followed by bacterial meningitis (33.8%), tuberculous meningitis (7.9%) and cerebral malaria (5.2%) in patients below 18 years of age.[1] Bokade *et al.* (2014) also showed viral encephalitis (46.59%) to be the most common cause of AFE; followed by pyogenic meningitis (22.16%), cerebral malaria (15.9%) and tubercular meningitis (15.35%).[2] However, in the study by Bansal *et al.* (2005) central nervous system infections (60%) were the most common cause; cases of tuberculous meningitis forming the majority (31% cases) followed by viral encephalitis 30%, bacterial meningitis 26% and others 11% (this was similar to our study).[5]

All our patients presented with fever of acute onset (< 14 days) and altered sensorium. GCS of less than 8 was seen in 27.5% (33 cases) in our study with mean of 9.02 and median of 9.0. This was consistent with other studies like those of Kumar *et al.* (2017) who (214 children with AFE in Eastern Bihar (March 2015 to February 2017)) noted the most common presenting complaints to be fever (100%) and altered sensorium (100%) with mean GCS of 9.6.[6] Also, the evaluation of clinical presentation by Anga et al. (2010) [study of AFE in children in Papua New Guinea; N = 149] revealed that 80% of children had fever of acute onset (less than 4 days) with 86% having convulsions.[7] The median GCS recorded in this study was 13.6 (higher than ours).[7] This difference may be accounted by the differences in presentation across the countries and the varying etiologies (bacterial meningitis, tuberculous meningitis and cerebral malaria seen by Anga G *et al.*; as against tubercular meningitis, viral encephalitis and bacterial meningitis seen in our study).[7] The spectrum of clinical profile of children presenting with acute febrile encephalopathy

studied by Singh *et al.* (2009) revealed that fever (100%) and altered sensorium (100%) were the most common presenting complaints with mean GCS of 9.6 (similar to ours).[8] Another common feature in our study was presence of convulsion/s at presentation (84 patients; 70%). This percentage was higher than that in studies by Kumar *et al.* (2017)[6] and Singh *et al.* (2009)[8], where convulsions were reported in only 50% of the patients; and was less than those seen by Anga G *et al.* (2010)[7], where convulsions were seen in 86% of patients. Our study showed meningeal signs in 38.3% cases; this was found to be lower than those seen by Kumar *et al.* (2017) – 50%[6], Singh *et al.* (2009) – 57%[7] and Anga *et al.* (2010) - 50%.[8] Such differences can be attributed to the different frequencies and the varying etiologies across various studies.

We had 20 deaths (mortality 16.7%) and 100 patients survived (83.3%). Out of the 100 children who survived, 46 patients improved with complete recovery while 54 cases had neuro-morbidity (40 incomplete recovery and 14 no recovery). Ahmad *et al.* (2017) in their study on 61 children with non-traumatic coma, showed that overall mortality was 33.9% with survival of 39 children (66.1%) and neuro-morbidity of 32%.[9] Among the 39 who survived, 48.7% were normal at discharge and 51.3% had varying degrees of disability.[9] As compared to our study, their mortality was higher with lower percentage of neuro-morbidity.[9] Bokade *et al.* (2014) (study on AFE; N=176) found mortality to be 19.31% with neurological sequelae in 26.7% subjects.[2] Maximum mortality was seen in viral encephalitis and least in pyogenic meningitis by Bokade *et al.* (2014).[2] Most sequelae were seen in cases of tuberculous meningitis and least in cerebral malaria by Bokade *et al.* (2014)[2] vis-a-vis our study which showed 100% sequelae in intracranial bleed followed by viral encephalitis (44.8% - incomplete recovery and 17.2% - no recovery seen in cases of viral encephalitis) and all cases of cerebral malaria recovered completely in our study. As compared to study by Bokade *et al.* (2014)[2], we had a slightly lower mortality rate but higher rates of neurological sequelae. This difference in mortality can be explained by the differences in the etiologies of AFE across various study populations and variable access to various diagnostic and treatment facilities. There was no association found between etiological diagnosis and recovery status in our study population.

Various factors affecting mortality studied by us included the age, gender, GCS, etiology, duration of hospital stay, duration of stay in PICU, mechanical ventilation and various clinical features (including convulsions). Of these the factors significantly increasing the mortality were - longer duration of hospital stay (≥ 28 days), longer duration of PICU stay (> 14 days), longer duration of mechanical ventilation (≥ 7 days) and lower GCS (< 8). Ahmad et al. (2017) studied risk factors affecting mortality and found age ≤ 3 years, poor pulse volume, hypotension, abnormal respiratory pattern, abnormal pupils, absent corneal reflex, abnormal extra-ocular movements, lower modified GCS and papilledema as high risk factors for mortality in children of non-traumatic coma.[9] Bokade *et al.* (2014) showed shock, severe anemia, bradycardia, GCS < 8 and refractory seizures to be significantly associated with mortality in children of AFE.[2] The different risk factors for mortality across different studies may be due to the differing patient populations, varying local epidemiology, different etiologies across various studies and varying availability of medical / intensive care. Table V summarizes the common etiologies, mortality and risk factors affecting mortality across various studies in comparison to our study.

India has one of the highest tuberculosis (TB) burdens worldwide. The burden of childhood TB is probably underestimated because majority of the children are sputum (microscopy / smear) negative.[11] Pediatric TB forms a minor fraction of total TB notifications annually (6% in 2019).[12] The exact prevalence of CNS TB in India is not known, but it accounts for an estimated 1% of all cases of TB.[13] TB can lead to tubercular meningitis (TBM), cerebral and spinal tuberculoma, myelitis and arachnoiditis. These are all more severe forms of TB and are associated with high incidence of death or disability. Case fatality rates for the most common form of CNS TB; i.e. TBM, are high. All forms of CNS TB can leave the survivors with long-term disabilities.[13] TBM classically presents as subacute or chronic meningitis with symptoms developing over days or weeks, however acute presentation is not unknown. Any patient with clinical features of meningitis (with or without altered sensorium or /and associated focal neurological deficits) for a period of 5 to 7 days or more need to be investigated for TBM. The common symptoms include headache, fever, vomiting, neck stiffness and

weight loss.[13] The traditional smear microscopy of CSF specimens has (extremely) low sensitivity and Xpert MTB / RIF is now a commercially available diagnostic test for Mycobacterium tuberculosis complex, which uses polymerase chain reaction (PCR) to test specimens for genetic material specific to MTB, and simultaneously detects a gene which confers resistance to rifampicin, rpoB. However, Xpert may be used only as an adjunctive test for tuberculous meningitis (TBM). A negative Xpert result does not rule out TBM, due to high number of false negatives. Hence, the decision to give anti-tubercular treatment (ATT) drugs should be based on the clinical features and the CSF profile (because delayed treatment has poor patient outcomes).[13] TB meningitis should be treated with standard first-line ATT for at least 9 months. Along with ATT, steroids are recommended for TB meningitis. Duration of steroid treatment should be for at least 4 weeks with further tapering as deemed appropriate.

We have evaluated the various demographics, clinical presentation, etiologies and outcome (mortality and neuro-morbidity) of children presenting with AFE. We have also tried to determine the risk factors affecting mortality. Limitations of our study includes our inability to study all the factors affecting mortality. Also, the details of the neuromorbidity and long-term neurological outcome/sequelae were not assessed by us.

We conclude that the most common etiology of children presenting with AFE to our institute was tubercular meningitis followed by viral encephalitis, bacterial meningitis and cerebral malaria. The mortality was 16.7% with 45% neuromorbidity.

CONCLUSION

Infectious causes were the commonest cause of AFE. AFE has a high rate of neuro-morbidity. Early identification of high risk factors may help to reduce the mortality.

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AUTHOR CONTRIBUTIONS

Dr. Mudita A Arora and Dr. Milind S. Tullu were equally involved in the conceptualization, collection of data, literature search and drafting the manuscript.

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